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Prequalification Team Inspection services
WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Finished Product Manufacturer

Part 1	**General information**
Manufacturers details	
Name of manufacturer	Lupin Limited
Corporate address of manufacturer	Lupin Limited Kalpataru Inspire, 3rd Floor, Off Western Express Highway, Santacruz (East), Mumbai, Maharashtra, 400055, India
Inspected site	
Name & address of inspected manufacturing site if different from that given above	Plot No: 6A, Sector 17, Special Economic Zone, Mihan Notified Area. Nagpur| 441108, India
Unit / block / workshop number	Unit-1 (Block-1)
Inspection details	
Dates of inspection	19 – 21 September 2018
Type of inspection	Initial GMP inspection
Introduction	
Brief description of the manufacturing activities	Oral Solid Dosage (OSD) Finished Pharmaceutical Product (FPP) manufacturing, Tablets and Capsules.
General information about the company and site	The Lupin Limited manufacturing facility is in Nagpur and has two Blocks; • Unit 1 Block 1 that is engaged in the manufacturing of Solid Oral Dosage Forms for the USA, European, Australian, and Canadian and ROW markets. Block 1 was constructed in 2013 for the manufacturing of Oral Solid Dosage Forms covers in total an area of 1, 17, 394 Sq. ft. • Block 2 which is a new OSD Facility, but not operational yet and therefore not part of the scope of the Inspection.
History	

No	Authority	Date	Status
1.	US-FDA	Sep-18	EIR awaited
2.	UK-MHRA	Jun-16	Certification Received
3.	Maharashtra State FDA	Apr-18	GMP Certificate No 6083877

Brief report of inspection activities undertaken – Scope and limitations	
Areas inspected	**Document reviewed including but not limited** o Organization Chart o Job descriptions for key personnel o Personnel training and hygiene o Product Quality Review o Quality Risk Management o Responsibilities of the quality units and production o Complaints and Recalls o Deviation control and change control o CAPA procedure o OOS and investigation o Material release o Self-inspection and vendor qualification o Validation and qualification o Equipment calibration o Data integrity o Sampling and testing of materials o Batch processing records o Materials management system o Purified water system o HVAC system **Site visit:** o Warehouse; o QC laboratories including chemical and microbiological; o Stability Chambers; o Block 1 manufacturing area; o Block 2 walk-through
Restrictions	The focus of the inspection was on Block 1; storage, production and quality control areas where WHO Pre-Qualification Applied for products (validation batches) was manufactured
Out of scope	Products not submitted to WHO for Prequalification
WHO products covered by the inspection	• TB 363, Para-Aminosalicylate Powder for Oral Solution 5.52 g; • HA703 Lamivudine/Tenofovir disoproxil fumarate Tablet, Film-coated 300mg/300mg; • HA720 Atazanavir (sulfate)/Ritonavir Tablet, Film-coated 300mg/100mg; • HA715 Emtricitabine/Tenofovir disoproxil fumarate Tablet, Film-coated 200mg/300mg
Abbreviations	**Meaning**
AHU	Air handling unit
ALCOA	Attributable, legible, contemporaneous, original and accurate
API	Active pharmaceutical ingredient
APR	Annual product review
APS	Aseptic process simulation

BMR	Batch manufacturing record
BPR	Batch production record
CC	Change control
CFU	Colony-forming unit
CIP	Cleaning in place
CoA	Certificate of analysis
CpK	Process capability
DQ	Design qualification
EDI	Electronic deionization
EM	Environmental monitoring
FMEA	Failure modes and effects analysis
FPP	Finished pharmaceutical product
FTA	Fault tree analysis
GMP	Good manufacturing practices
GPT	Growth promotion test
HEPA	High efficiency particulate air
HPLC	High performance liquid chromatography (or high performance liquid chromatography equipment)
HVAC	Heating, ventilation and air conditioning
IQ	Installation qualification
LAF	Laminar air flow
LIMS	Laboratory information management system
MB	Microbiology
MBL	Microbiology laboratory
MF	Master formulae
MFT	Media fill Test
MR	Management review
NC	Non conformity
NRA	National regulatory agency
OQ	Operational qualification
PHA	Process hazard analysis
PLC	Programmable logic controller
PM	Preventive maintenance
PQ	Performance qualification
PQR	Product quality review
PQS	Pharmaceutical quality system
PW	Purified water
QA	Quality assurance
QC	Quality control
QCL	Quality control laboratory
QMS	Quality management system
QRM	Quality risk management
RA	Risk assessment
RCA	Root cause analysis

RO	Reverse osmosis
SIP	Sterilization in place
SMF	Site master file
SOP	Standard operating procedure
URS	User requirements specifications
UV	Ultraviolet-visible spectrophotometer
WFI	Water for injection

Part 2	**Summary of the findings and comments**

1. Pharmaceutical quality system

A pharmaceutical quality system (PQS) was established, with Quality Manual, Policies and written procedures covering essential GMP principles for the site. The Quality Manual was prepared based on global company policies. Management Review meetings were held monthly in accordance and minutes provided to the relevant Global Department. QA was responsible for compiling all data and information and organize and maintain minutes of the meetings. PQS included both corporate and site-specific procedures. Procedures that were reviewed and discussed during the inspection were generally presented promptly. Calibre-elog is used for most of the QMS.

Annual product quality reviews were performed annually on a rolling basis and QA was responsible for approving the reports and monitoring the process which had to be completed within two calendar months from end of product review period. Only three validation batches of each product have been manufactured as commercial production has not yet commenced.

A Corporate QRM SOP described in detail the principles for identifying different risks pertaining to product/ specific process, system, equipment and evaluation of the impact on product quality, service and patient health. QRM was widely applied on all manufacturing operations including but not limited to change control and deviation management, production and complaints.

The procedure in place for change management adequately described the process for initiating temporary and permanent changes, defined roles, responsibilities and requirements for management of changes and tracking their effectiveness. Changes and Deviations were registered and managed using Calibre-elog.

Calibre e-log was used for data management accessing the audit trails. The computer administrator based in Lupin' HQ had access to change date/time stamp.

The deviation list pertaining to the WHO products was presented. It related to deviations prior or during manufacturing of Exhibit Batches.

- DEV-NA-204-17-0005, BMR of Atazanavir Sulphate and Ritonavir 300 mg / 100 mg tablets;
- DEV-NA-204-17-0006, Atazanavir and Ritonavir 300 mg / 100 mg tablets, batch M790294 in view of appearance of a horizontal crack line on coated tablet surface;
- DEV-NA-204-17-0010, Atazanavir and Ritonavir 300 mg / 100 mg tablets, batch M790629 in view of appearance of a horizontal crack line on coated tablet surface.

Root cause investigations were performed and in the case of the BMR immediate correction took place. Exhibit Batches for Atazanavir Sulphate and Ritonavir 300 mg / 100 mg tablets were rejected due to the appearance issue and new batches were manufactured applying the CAPA. The second set of batches manufactured was released for Stability testing.

The SOP for CAPA management includes Effectiveness Monitoring, generally for a period of 2 years however this can vary from case to case and is performed by the Initiator. CAPA Trending is performed by QA. Quarterly Reports are prepared as per respective SOP`s and annually discussed at Manage Review Meeting.

The quality metrics were analysed by Site Management every quarter i.e. Jan – March `18. Management Review agenda`s and minutes are provided to Corporate QA.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

2. Good manufacturing practices for pharmaceutical products

Basic principles of good manufacturing practices were generally described and implemented. Manufacturing processes were adequately defined and documented in BMRs and BPRs. Required resources were available, including adequate premises, equipment and utilities. Appropriately qualified personnel were employed.

3. Sanitation and hygiene

Premises and equipment were clean in accordance with established SOP`s, good housekeeping was reflected throughout the site. Spot checks on rodent traps and insecticutors of the external areas and entrances were made. Human resources were responsible for monitoring and controlling the third party providing pest control services

4. Qualification and validation

The key principles of qualification and validation program were defined and documented in the Validation Master Plan. The VMP of the site addressed validation/qualification activities including but not limited to equipment, utilities, processes and cleaning, analytical methodology, vendors and computerized systems.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

5. Complaints

The company had in place a Corporate SOP on registering, investigating and monitoring complaints as well as on handling and disposal of non-conforming products. Periodic reports are to be issued to Corporate QA.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

6. Product recalls

A Corporate SOP for Product Recall procedure was available. Mock recalls were documented and performed on an annual basis.

7. Contract production, analysis and other activities

Technical Quality Agreements were in place with contract laboratories as well as the availability of comprehensive audit reports. SOP CQA-064-00 detail Contract Laboratory Testing, requirements.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

8. Self-inspection, quality audits and suppliers' audits and approval

Audits were performed centrally by Global Operations Audit Team.

Vendor qualification procedure was discussed. A process flow chart was part of the procedure. In general, the procedure was adequate except that before on-site assessment of API vendors, APIs are used in the exhibit batches. Clear provision should be made to ensure that exhibit batches are not commercialised before an on-site assessment.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

9. Personnel

Organization charts were available reflecting administrative structure. In general personnel met during the inspection appeared aware of the basic principles of GMP. Job descriptions of the Head of Quality (QA) and Senior Manager Quality Control were reviewed and in place.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

10. Training

Training of personnel was performed and managed using L2LMS Training Management System. Respective head of departments was responsible for grouping personnel together according to job profile and training needs. Training sessions were prepared based on a matrix which was paper based CQA-018/F1-03. Plans, material and training records of personnel were demonstrated with L2LMS. Induction training takes place and assessment records were available. Further comprehensive list of relevant topics related to GLP/GMP/GXP/ 21 CFR parts 10 &11, good chromatographic techniques, health and hygiene and data integrity was provided. Training was class room based where required by relevant experts from the site or Corporate HQ and in addition electronically in line with required topics/material.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

11. Personal hygiene

Instructions and pictorials to be followed were sufficiently clear when it came to personal hygiene. For new personnel including contract personnel, medical examinations were foreseen before joining the company and yearly afterwards Spot checks on medical records of personnel were performed.

12. Premises

Two Blocks were located on the site; currently production takes place in Block 1. Block 2 is a newly set-up and not operational yet. Block 1 ground floor houses production activities starting from dispensing of materials, sifting, granulation, blending, compression, coating, blister packaging, bottle packaging and secondary packaging areas.

The first-floor houses part of the administration activities, analytical quality control laboratory, stability chambers and the second floor, the service area and Microbiological laboratory. There was no pouch filling area in block 1 and it will be created in block 2 which is not ready for this inspection.

SAP was used for material management, warehouse management, weighing and dispensing. Data acquisition system (DAS) was used in the warehouse for monitoring environmental monitoring. A cold storage area (between 2 and 8 ˚C) is also provided inside the warehouse for storing of temperature sensitive materials.

The production area was classified as ISO 8; the corridor is over pressurised (40 pascal) as compared to core processing areas (30 pascal). In block 1, there are no change rooms and or airlocks provided prior to entry into the core processing areas. In the production area, PLC/HMI based production equipment and environmental monitoring system (EMS) was used.

Raw water from MADC (Maharashtra Airport Development) was used as input water for potable water.

Laboratories were well managed, neat; the Analytical Laboratory area was limited however the new facility Block 2 was designed to accommodate the matter.

13. Equipment

In general production equipment was appropriate for the manufacture of solid dosage forms. Some deficiencies were noted in terms of Purified Water System monitoring and HVAC periodic requalification and daily monitoring, Qualification and Validation.

A QC Laboratory Equipment List was available; Calibration, Qualification and Maintenance were managed with Calibre e-log. Laboratory Equipment/Instruments and Stability Chambers were labeled indicating the details; equipment numbers, calibration, maintenance and validation status. The maintenance operational list for the HPLCs was comprehensive and included items such as the Clean Degasser Chambers, Pump Head and Leak Sensor function.

Schematic diagram of purified water distribution system (Nagpur/Eng/16/09-09 dated 5/10/2017) was reviewed. The system was equipped with double pass reverse osmosis, metabisulphite dosing, EDI and thermal sanitization (not less than 80FC for 40 minutes). The insulated storage tank of 2000L was used to store purified water. The sanitization was done once every month (80C for 60 minutes). In addition, ozone sanitization (water based) was used once per day. Total of 17 user points are in the manufacturing and laboratory area whereas 7 sampling points. For return loop, ozone meter, temperature, conductivity and TOC were used.

Production core processing areas in Block 1 were maintained negative to adjacent corridor; no leakage was seen on the ducts inside

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

14. Materials

There was a procedure in place describing receipt and storage of raw materials. A GRN check list was used for receipt of raw materials. Material stock and status were managed via SAP. A unique material code was assigned to each material in the system. Procedures for material sampling and dispensing were available. Temperature was monitored and daily recorded. The placement of the loggers does not appear to cover all critical areas given the temperature profile of the location.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

15. Documentation

A documentation system was in place. Procedures defined and supported manufacturing and quality control operations. In documents were approved, reviewed, signed and dated by appropriate responsible persons, kept up to date by periodic review. The QC Laboratories SOPs reviewed was paper based and managed as such. Specifications and testing procedures were available, controlled and the manner of issuing it compliant.

Executed Batch Document of Emtricitabine (3TC) and Tenofovir (TDF) 200 mg / 300 mg tablets was reviewed. Codes, dates, checks and signatures were in place, SAP codes of API`s confirmed correct vendors.

Analytical Reports reviewed refer COA TDF Batch received from Laurus with Batch no. The report contained required details e.g. Balance Serial recorded to be calibrated before use. Analytical Report of COA Emtricitabine batch no. was also reviewed and the same level of detail was displayed

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

16. Good practices in production

Generally, operations in the warehouse and productions area seemed to be acceptable and the production area was found clean and tidy as noted during inspection. Status of Emtricitabine was verified using the handheld device (in quality inspection due to retesting). The status was cross verified from the SAP and was found satisfactory. The status of approved vendors was also verified through SAP system for Lamivudine (Hetero Unit-IX) and Sodium PAS (Biochemical). Primary packaging materials were sampled and dispensed under RLAF. The sampling was performed using AQL standard (ISO 2859-1) to select number of containers required to be sampled.

Two balances of different capacity were used for the verification of dispensed materials. Return air risers were obstructed by vacuum cleaner and panel of sifter. From the discussion with production operator of the sifting area, it appeared that he does not use dust collector during sifting of the materials.

Quarantine blend area was access control, although the room was access control, the cages used to store blended materials were not locked. Tool room was access control however noted that time zone was not locked and was subjected for changes.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

17. Good practices in quality control

Quality control laboratories were separated from production areas. Analytical QC laboratories as well as the Microbiological laboratory were visited. The QC lab was well organized and equipped. Samples for testing were received, issued, documented and well managed. Analytical equipment/instruments including the stability chambers were Qualified/Calibrated and Maintained. Logbooks for use and maintenance of equipment were presented. Chromeleon software was used to collect, manage, and report chromatography test results for GC and HPLC equipment. Different roles and access rights were established and implemented accordingly. Analyst demonstrated HPLC sequence data and audit trails of analysis.

Reference, impurities standards, reagents and including solutions were kept in conditions prescribed and their consumption documented. An in-house Shelf-life was allocated after opening.

Practices in the Microbiological laboratory were generally compliant. Procedures and records for preparation of culture media, growth promotion testing and storage of materials and reagents were reviewed. Cultures are bought and tested with the Vitek2 Compact I-086. The Microbiological Testing room is equipped with two MAL pass boxes and PAL airlock is in place. Daily print outs of temperature of equipment such as the refrigerators are done. A usage log is kept for the LAF preparation booth and the maintenance of this HVAC system (especially HEPA filter integrity) forms part of the Maintenance Log. Seven Incubators are present in the laboratory and a Vertical Autoclave E-022. The Qualification and re-Qualification records of the Autoclave were available upon request.

Stability Chambers covering all temperatures and humidity for the required WHO zones and other are available. The chambers have ample storage place and samples are labelled appropriately. Chambers E-031, E-032, E-033 were reviewed and were appropriately labelled with Qualification, Calibration Labels as well as external environmental monitoring displays. The chambers are 6 monthly reviewed by Maintenance and re-Qualified annually. Access is controlled with access cards issued to three qualified personnel.

It was noted though that the stability chambers are used for storage of analytical samples for testing. Note the opening and closing of these chambers may negatively influence the environmental conditions. It was confirmed that Block 2 laboratories were designed with adequate storage place for testing/tested samples.

Weights used for daily calibration of Balances, 1 mg - 200 g set E2 was observed and COA of annual external calibration was available.

The Corporate SOP for Reduced Testing (Analytical), point 5.4.2 describes that for API`s, Inactive Pharmaceutical Ingredients and other raw materials the first 10 batches/consecutive supplies have to be fully tested. Based on reviews of information by Regulatory/Subject Matter Experts, QA shall decide on reduced testing. Irrespective of reduced testing one batch will undergo full testing every year. If any previous testing of material from a supplier had OOS test results, full testing of all drums shall take place. The effectiveness of Reduced Testing is reviewed at specified frequencies.

The issues related to this section have been adequately addressed by the manufacturer, and the same shall be verified during future inspections.

Part 3	**Conclusion – Inspection outcome**

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection, including the observations listed in the Inspection Report, ***Lupin Limited***,located at ***Plot No: 6A, Sector 17, Special Economic Zone, Mihan Notified Area. Nagpur, India*** was considered to be operating at an acceptable level of compliance with WHO GMP Guidelines.

All the non-compliances observed during the inspection that were listed in the full report as well as those reflected in the WHOPIR, were addressed by the manufacturer, to a satisfactory level, prior to the publication of the WHOPIR.

This WHOPIR will remain valid for 3 years, provided that the outcome of any inspection conducted during this period is positive.

Part 4	List of WHO Guidelines referenced in the inspection report

1. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. ***Short name: WHO TRS No. 986, Annex 2***
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/
2. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. ***Short name: WHO GMP for APIs*** or ***TRS No. 957, Annex 2***
   http://www.who.int/medicines/publications/44threport/en/

3. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2
   Short name: WHO TRS No. 970, Annex 2
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/
4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4
   Short name: WHO TRS No. 929, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1

5. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty Second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. **Short name: WHO TRS No. 1010, Annex 8**
   http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/

6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4
   Short name: WHO TRS No. 937, Annex 4
   http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1

7. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1
   Short name: WHO GPPQCL Guidelines or ***TRS No. 957, Annex 1***
   http://www.who.int/medicines/publications/44threport/en/

8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2
   Short name: WHO TRS No. 957, Annex 2
   http://www.who.int/medicines/publications/44threport/en/

9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6
   Short name: WHO TRS No. 961, Annex 6
   http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7
    Short name: WHO TRS No. 961, Annex 7
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9. ***Short name: WHO TRS No. 961, Annex 9***
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3
    Short name: WHO TRS No. 943, Annex 3
    http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1

13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2
    Short name: WHO TRS No. 961, Annex 2
    http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2. ***Short name: WHO TRS No. 981, Annex 2*** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3. ***Short name: WHO TRS No. 981, Annex 3*** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/

16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14. ***Short name: WHO TRS No. 961, Annex 14*** http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1

17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3. ***Short name: WHO TRS No. 992, Annex 3*** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4. ***Short name: WHO TRS No. 992, Annex 4*** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5. ***Short name: WHO TRS No. 992, Annex 5*** http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

20. WHO Recommendations for quality requirements when plant – derived artemisin is used as a starting material in the production of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6
Short name: WHO TRS No. 992, Annex 6
http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf

21. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5
Short name: WHO GDRMP or ***WHO TRS No. 996, Annex 5***
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

22. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10
Short name: WHO TRS No. 996, Annex 10
http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf